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Type 2 diabetes is associated with impaired endothelium-dependent, flow-mediated dilation, but impaired glucose metabolism is not

The Hoorn Study

Ronald M.A. Henry^{a,b}, Isabel Ferreira^a, Piet J. Kostense^{a,c}, Jacqueline M. Dekker^a,
Giel Nijpels^a, Robert J. Heine^d, Otto Kamp^b, Lex M. Bouter^a, Coen D.A. Stehouwer^{a,b,e,*}

^a Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, The Netherlands

^b Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, The Netherlands

^c Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

^d Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands

^e Department of Internal Medicine, VU University Medical Center, Amsterdam, The Netherlands

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Abstract

Background: Type 2 diabetes (DM2) and impaired glucose metabolism (IGM) are associated with an increased cardiovascular disease risk. Impaired endothelial synthesis of nitric oxide (NO) is an important feature of atherothrombosis and can be estimated from endothelium-dependent flow-mediated dilation (FMD). It is controversial whether or not FMD is impaired in DM2 and IGM. We investigated this issue in a population-based setting. **Methods and results:** In the study population ($n = 650$; 246 with normal glucose metabolism (NGM), 135 with IGM and 269 with DM2; mean age: 67.6 years), FMD and endothelium-independent nitroglycerine-mediated dilation (NMD) were ultrasonically estimated from the brachial artery and expressed as the absolute change in diameter in mm. The increase in diameter (mean \pm standard deviation) in NGM, IGM and DM2 was 0.19 ± 0.15 , 0.19 ± 0.18 and 0.13 ± 0.17 for FMD and 0.45 ± 0.21 , 0.43 ± 0.24 and 0.45 ± 0.25 for NMD. After adjustment for age, sex, baseline diameter and percentage increase in peak systolic velocity, DM2, as compared to NGM, remained associated with impaired FMD (regression coefficient β (95% CI) as compared to NGM, -0.06 mm (-0.09 to -0.03). IGM was not associated with impaired FMD (β , 0.01 mm (-0.02 to 0.04)). Additional adjustment for conventional cardiovascular risk factors did not alter these associations. Hyperglycemia or hyperinsulinemia explained 2% of the association between DM2 and FMD. NMD was not associated with glucose tolerance. **Conclusions:** This study shows that DM2 is independently associated with impaired FMD. Hyperglycemia and hyperinsulinemia contribute minimally to this association. Impaired FMD may therefore, in part, explain the increased cardiovascular disease risk in DM2, whereas the normal FMD in IGM suggests that other forms of endothelial dysfunction are important in explaining the increased cardiovascular disease risk in IGM.

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1. Introduction

Cardiovascular disease is the major cause of mortality in type 2 diabetes (DM2) [1]. An increased cardiovascular disease risk is already apparent in impaired glucose metabolism (IGM), i.e., impaired fasting glucose and (or) impaired glucose tolerance [2], and cannot be fully explained by conventional cardiovascular risk factors associated with de-

teriorating glucose tolerance, such as hypertension, obesity and dyslipidemia [3].

It is currently hypothesized that DM2 and IGM are associated with impaired endothelial synthesis of nitric oxide (NO), and that this may explain, at least in part, the increased cardiovascular disease risk associated with these conditions [4,5]. Indeed, endothelium-derived NO is an important anti-atherosclerotic and anti-thrombotic mediator, and impaired availability of endothelium-derived NO is thought to play an important role in both early and late stages of atherothrombotic disease [6]. Endothelial synthesis of NO can be estimated from vasodilation and (or) flow increase

* Corresponding author. Tel.: +31-20-444-0629;

fax: +31-20-444-4313.

E-mail address: cda.stehouwer@vumc.nl (C.D.A. Stehouwer).

in response to stimuli such as acetylcholine, bradykinine or increased shear stress, responses that are collectively referred to as endothelium-dependent vasodilation.

Studies of endothelium-dependent vasodilation in DM2 and IGM have yielded contradictory results [7–28]. Both impaired [7–14,16,18,20–28] and normal [15,19] endothelium-dependent vasodilation have been reported in DM2 and impaired glucose tolerance, whereas some studies have reported that both endothelium-dependent and -independent responses are impaired in DM2, suggesting impaired function of vascular smooth muscle rather than the endothelium [8,12,14,20,21,24]. These inconsistent results may have resulted from selection, as these studies have been relatively small and have not been population-based. In view of these considerations, we investigated, in a population-based cohort, associations between DM2 and IGM, and impaired endothelium-dependent or -independent vasodilation, as measured by brachial artery ultrasonography.

2. Methods

2.1. Study population

For the present investigation, we used data from the 2000 Hoorn Study follow-up examination [29] and the Hoorn Screening Study [30], both of which were population-based. The exact sampling procedures have been described elsewhere [29,30]. Briefly, the Hoorn Study is a study of glucose metabolism in the general population ($n = 2484$), which started in 1989. In 2000, a follow-up examination was carried out among all surviving participants. We invited all those who had diabetes, as determined by an oral glucose tolerance test, or who were treated for diabetes at the 1996 follow-up ($n = 176$). We also invited random samples of individuals with normal glucose metabolism (NGM) ($n = 705$) and IGM, either impaired fasting glucose or impaired glucose tolerance ($n = 193$). Of 1074 individuals thus invited, 648 (60%) participated. Additionally, to increase the number of individuals with DM2, we invited 217 individuals from the Hoorn Screening Study [30], a screening study for DM2 in the general population, 188 (87%) of whom participated. Data on 14 individuals were missing due to logistical problems. The population ($n = 822$) was categorized according to the WHO-1999 criteria [31], and thus consisted of three groups: 290 with NGM, 187 with IGM, and 345 with DM2. The study was approved by the local ethics committee. All participants gave their written informed consent.

2.2. Non-participants

Among the 455 non-participants (53% women), 13% were complete non-responders. The remaining non-participants gave various reasons not to participate: lack of interest (30%); co-morbidity (23%); age (7%); unwillingness to

travel (6%); participation too time-consuming (6%); and miscellaneous reasons (15%).

2.3. General procedures

All individuals underwent the ultrasound examination according to the guidelines of the International Brachial Artery Reactivity Task Force [32].

The diameter of the right brachial artery (20 mm proximal to the antecubital fossa) was assessed with the use of an ultrasound scanner equipped with an 7.5 MHz linear probe (350 series, Pie Medical, Maastricht, The Netherlands). The scanner was connected to a PC equipped with vessel wall movement detection software and an acquisition system (Wall Track System, Pie Medical, Maastricht, The Netherlands). This set-up enables measurement of diameter, as described in detail elsewhere [33–35]. Blood flow (peak systolic velocity) was estimated by pulsed-wave Doppler from a sample volume in the center of the artery at a 60° angle. To secure the ultrasound image and measurement position throughout the study, we used an stereotactic probe-holding device, while the subject's arm was positioned over a foam cast to inhibit movement.

2.3.1. Determination of endothelium-dependent flow-mediated dilation (FMD)

The measurement protocol has been described in detail [36]. Briefly, baseline diameter (mean of three measurements) and peak flow velocity (mean of two measurements) were determined. A pressure cuff, placed on the forearm, was then automatically inflated and kept constant at supra-systolic pressure (brachial systolic pressure +100 mmHg) in order to induce forearm ischemia. After 5 min the cuff was released, which was followed by an increase in blood flow. This increase in blood flow increased shear stress, which served as the stimulus for FMD. After cuff release, maximum peak flow velocity was measured within 15 s, and diameter at 45, 90, 180 and 300 s. The maximum diameter in any of these four measurements was used in the statistical analysis.

2.3.2. Determination of endothelium-independent nitroglycerine-mediated dilation (NMD)

Next, 15 min of rest were taken to re-establish baseline conditions. Baseline diameter (mean of three measurements) and peak flow velocity (mean of two measurements) were re-determined. Nitroglycerin (400 µg, Nitrolingual Spray, Pohl-Boskamp, Germany) was then sublingually administered; after 5 min, diameter (mean of three measurements) and peak flow velocity (mean of two measurements) were again determined.

2.4. Reproducibility

Reproducibility was assessed in ten individuals (five men; 58.2 ± 9.5 years) who were examined twice, 2 weeks apart.

The intra-observer intersession coefficients of variation [CV = (standard deviation of the mean difference/ $(\sqrt{2} \times$ pooled mean)] were 4.3% for diameter, 14.7% for FMD and 10.3% for NMD (the latter two expressed as absolute diameter change).

2.5. Other measurements

Health status, medical history, current medication use and smoking habits were assessed by a questionnaire [29]. Glucose, glycated hemoglobin, insulin, creatinine, urinary albumin, serum total, high-density and low-density lipoprotein cholesterol and triglycerides were determined as described elsewhere [29,37]. Resting electrocardiograms were automatically coded according to the Minnesota Code [38], and body mass index and waist-to-hip ratio were calculated. Brachial systolic and diastolic pressures were assessed in the left upper arm at 5-min intervals with an oscillometric device (Collin Press-Mate, BP-8800, Komaki-City, Japan). Hypertension, prior cardiovascular disease and (micro)-albuminuria were defined as described previously [37,39].

2.6. Statistical analyses

All analyses were carried out with SPSS (SPSS, Chicago, USA). Trend analyses were carried out by one-way analysis of variance. We used multiple linear regression analysis to investigate the associations between glucose tolerance and FMD. All associations were first analyzed without

any adjustments and then with adjustment for potential confounders. In the adjusted models, age, sex, baseline diameter and the increase in shear stress (estimated from the percentage increase in peak systolic velocity) were considered first [40,41]. We used an interaction term to investigate whether the association between FMD and glucose tolerance differed according to sex [26]. *P*-values <0.05 were considered statistically significant, except for interaction analyses, where we used *P* < 0.10.

3. Results

3.1. Ultrasonography

Of the 822 participants, qualitatively satisfactory ultrasound examinations were obtained in 650 individuals. Data were missing for logistical reasons (*n* = 18); technical reasons (*n* = 8); and poor definition of the arterial wall (*n* = 107) due to obesity (*n* = 85 (23 with NGM, 26 with IGM and 36 with DM2; body mass index 30.4, 30.7 and 32.7 kg/m², respectively), body mass index of those with qualitatively satisfactory ultrasound examination versus those without, 26.8 ± 3.2 kg/m² versus 31.1 ± 5.4 kg/m², *P* < 0.001) or the inability to remain motionless due to musculoskeletal disorders (*n* = 39).

3.2. Baseline characteristics

Table 1 shows the characteristics of the study population.

Table 1
Characteristics of the study population according to glucose tolerance status

	NGM	IGM	DM2	<i>P</i> (trend)
<i>N</i> (m/f)	246 (119/127)	135 (71/64)	269 (139/130)	–
Age (years)	67.8 ± 5.6	69.1 ± 5.9	66.5 ± 8.1 ^a	0.185
Systolic blood pressure (mmHg)	135 ± 19	143 ± 17 ^b	148 ± 19 ^{a,b}	<0.001
Diastolic blood pressure (mmHg)	74 ± 9	78 ± 9 ^b	79 ± 9 ^b	<0.001
Hypertension (%)	53	71 ^b	81 ^b	<0.001
Antihypertensive medication (%)	22	30 ^b	50 ^b	<0.001
Total cholesterol (mmol/l)	5.86 ± 1.01	5.92 ± 0.99	5.56 ± 1.07 ^{a,b}	0.005
HDL cholesterol (mmol/l)	1.51 ± 0.41	1.43 ± 0.41	1.26 ± 0.35 ^{a,b}	<0.001
LDL cholesterol (mmol/l)	3.77 ± 0.88	3.78 ± 0.92	3.47 ± 0.93 ^{a,b}	0.003
Triglycerides (mmol/l)	1.2 (0.9 – 1.6)	1.4 (1.0 – 1.9) ^b	1.6 (1.2–2.3) ^{a,b}	<0.001
Lipid-lowering medication (%)	11	15	20 ^b	0.039
Fasting glucose (mmol/l)	5.42 ± 0.37	6.05 ± 0.52 ^b	7.61 ± 1.65 ^{a,b}	<0.001
Post-load glucose (mmol/l)	5.59 ± 1.12	7.99 ± 1.65 ^b	11.57 ± 2.76 ^{a,b}	<0.001
Glycated hemoglobin (%)	5.86 ± 0.41	5.83 ± 0.39	6.57 ± 0.90 ^{a,b}	<0.001
Insulin (pmol/l)	46.0 (34.3–59.0)	66.0 (50.0–88.0) ^b	82.5 (55.0–109.8) ^{a,b}	<0.001
Body mass index (kg/m ²)	25.9 ± 3.2	27.3 ± 3.3 ^b	28.5 ± 3.8 ^{a,b}	<0.001
Waist-to-hip ratio	0.89 ± 0.09	0.94 ± 0.08 ^b	0.96 ± 0.10 ^{a,b}	<0.001
Current smoking (%)	16	16	12 ^{a,b}	0.537
Serum creatinine (μmol/l)	95 ± 14	95 ± 15	95 ± 19	0.847
(Micro-)albuminuria (%)	9	15	19 ^b	<0.001
Prior cardiovascular disease (%)	41	49	51 ^b	<0.001

Mean ± standard deviation or median (inter-quartile range). NGM: normal glucose metabolism; IGM: impaired glucose metabolism; DM2: type 2 diabetes.

^a *P* < 0.05 as compared to IGM.

^b As compared to NGM *P* < 0.05. *P* for trend tested by ANOVA.

Table 2
Right brachial artery variables according to glucose tolerance

	NGM	IGM	DM2
Diameter (mm)			
Baseline	4.55 ± 0.76 (2.87 to 7.07)	4.67 ± 0.72 (2.84 to 7.60)	4.78 ± 0.74 (2.94 to 7.22) ^{a,b}
After FMD	4.74 ± 0.75 (3.09 to 7.14)	4.86 ± 0.73 (3.09 to 7.67)	4.91 ± 0.73 (2.87 to 7.38) ^{a,b}
After NMD	4.99 ± 0.77 (3.17 to 7.27)	5.09 ± 0.72 (3.27 to 7.70)	5.22 ± 0.72 (3.37 to 7.50) ^{a,b}
Absolute change in diameter (mm)			
After FMD	0.19 ± 0.15 (−0.11 to 1.02)	0.19 ± 0.18 (−0.02 to 0.93)	0.13 ± 0.17 (−1.24 to 0.69) ^{a,b}
After NMD	0.45 ± 0.21 (0.00 to 1.42)	0.43 ± 0.24 (−0.81 to 1.21)	0.45 ± 0.25 (−1.00 to 1.36)
Percentage change in diameter (%)			
After FMD	4.47 ± 3.78 (−1.82 to 29.50)	4.23 ± 3.92 (−0.43 to 19.15)	2.96 ± 3.66 (−22.93 to 16.64) ^{a,b}
After NMD	10.29 ± 5.49 (−0.05 to 41.74)	9.64 ± 5.48 (−14.32 to 29.63)	9.88 ± 6.75 (−18.55 to 40.10)
Peak systolic velocity (cm/s)			
Baseline	56 ± 13 (31 to 114)	58 ± 13 (26 to 97)	60 ± 14 (32 to 115) ^{a,b}
After reactive hyperemia	108 ± 29 (52 to 217)	105 ± 22 (51 to 175)	105 ± 25 (56 to 195)
% increase	95 ± 49 (4 to 383)	84 ± 37 (4 to 221) ^a	77 ± 38 (4 to 188) ^{a,b}

Results are expressed as mean ± standard deviation (range). FMD and NMD, respectively stand for flow-mediated dilation and nitroglycerine-mediated dilation.

^a $P \leq 0.01$ as compared to NGM.

^b $P \leq 0.03$ as compared to IGM; other P -values were ≥ 0.12 .

3.3. FMD and NMD

Individuals with impaired fasting glucose ($n = 48$) and impaired glucose tolerance ($n = 87$) did not significantly differ from each other with regard to FMD ($P = 0.42$), NMD ($P = 0.29$) or other cardiovascular risk factors and were therefore combined in the analyses.

Baseline diameter increased with deteriorating glucose tolerance, and percentage increase in peak systolic velocity decreased (Table 2). After adjustment for age, sex, baseline diameter and percentage increase in peak systolic velocity, DM2, as compared to NGM, was associated with smaller FMD, but IGM was not (Table 3, model 2). Further adjustment for potential confounders did not materially affect these estimates (Table 3, models 3–8), even though, as expected, the presence of cardiovascular risk factors in general was associated with smaller FMD (Table 4).

NMD was not associated with glucose tolerance in unadjusted (Table 2, Fig. 1) or adjusted analyses (data not shown).

3.4. Additional analyses

The association between FMD and glucose tolerance did not differ according to sex ($P_{\text{interaction}} = 0.47$). Our results were not materially altered if we simultaneously added all variables from model 1–8 into one statistical model (data not shown). Our results were also not materially altered if we compared those who were examined in the morning (08:00 h, completely fasting) to those examined in the afternoon (12:00 h, provided with a light breakfast at 08:00 h). The percentages of fasted/non-fasted individuals did not statistically significantly differ between NGM, IGM and DM2 (data not shown).

To estimate the contribution of hyperglycemia and of hyperinsulinemia to the smaller FMD associated with DM2, we compared the above analyses with those adjusted for HbA1c ($n = 269$) (or fasting glucose ($n = 269$) or post-load glucose ($n = 222$, as 47 individuals with previously diagnosed DM2 did not undergo the oral glucose tolerance test) and for fasting insulin concentrations ($n = 259$, as 10

Table 3
Flow-mediated dilation according to glucose tolerance: adjusted analyses

Model	Added variables	IGM	DM2
1	–	−0.001 (−0.04 to 0.04)	−0.06 (−0.09 to −0.03)
2	Age, sex, baseline diameter, flow increase	0.01 (−0.02 to 0.04)	−0.06 (−0.09 to −0.03)
3	Model 2 + prior cardiovascular disease	0.02 (−0.02 to 0.05)	−0.05 (−0.08 to −0.02)
4	Model 2 + hypertension	0.01 (−0.02 to 0.05)	−0.05 (−0.08 to −0.02)
5	Model 2 + lipid-lowering medication	0.01 (−0.02 to 0.05)	−0.05 (−0.08 to −0.03)
6	Model 2 + body mass index	0.01 (−0.03 to 0.04)	−0.06 (−0.09 to −0.03)
7	Model 2 + (micro-)albuminuria	0.01 (−0.02 to 0.05)	−0.05 (−0.08 to −0.03)
8	Model 2 + smoking	0.01 (−0.02 to 0.04)	−0.06 (−0.09 to −0.03)

Results are expressed as betas and 95% confidence intervals, with NGM as reference category. The absolute change in diameter, in millimeters, was the dependent variable. Similar results were obtained when model 2 was additionally adjusted for systolic or diastolic pressure, lipid profile, waist-to-hip ratio, or serum creatinine (data not shown).

Table 4

Cross-sectional associations between flow-mediated dilation and cardiovascular risk factors for the entire study population

	Standard deviation	Standardized β	P-value
Age	6.9 years	−0.033	<0.001
Risk factors adjusted for age			
Sex	Men vs. women	−0.0047	0.476
Fasting glucose	1.5 mmol/l	−0.020	0.002
Post-load glucose	2.6 mmol/l	−0.011	0.165
Glycated hemoglobin	0.8%	−0.019	0.005
Insulin	51 pmol/l	−0.013	0.061
Systolic pressure	19 mmHg	−0.029	<0.001
Diastolic pressure	9 mmHg	−0.024	<0.001
Hypertension	Yes vs. no	−0.024	<0.001
Antihypertensive medication	Yes vs. no	−0.027	<0.001
Total cholesterol	1.0 mmol/l	−0.005	0.489
High-density lipoprotein cholesterol	0.40 mmol/l	0.006	0.360
Low-density lipoprotein cholesterol	0.9 mmol/l	0.009	0.189
Triglycerides	0.9 mmol/l	−0.014	0.029
Lipid-lowering medication	Yes vs. no	−0.013	0.049
Body mass index	3.6 kg/m ²	−0.016	0.018
Waist-to-hip ratio	0.09	−0.010	0.133
Serum creatinine	16 μ mol/l	0.012	0.078
(Micro-)albuminuria	Yes vs. no	−0.017	0.011
Smoking	Yes vs. no	−0.020	<0.001
Prior cardiovascular disease	Yes vs. no	−0.020	0.004

The regression coefficients are expressed as standardized β (in mm) per change of 1 standard deviation of the independent variable to facilitate direct comparison.

individuals were on insulin therapy). These adjustments explained at most 2% of the observed associations (data not shown). Conversely, the associations between either fasting glucose, HbA1c or insulin on the one hand and FMD on

the other (Table 4) were entirely accounted for by DM2 in a model adjusted for sex, age, baseline diameter and increase in peak systolic velocity (data not shown).

4. Discussion

This population-based study of glucose tolerance and FMD had three main findings. First, after adjustment for age, sex, baseline diameter and increase in peak systolic velocity, DM2, as compared to NGM, was associated with smaller FMD, whereas IGM was not. These findings were independent of other cardiovascular risk factors. Second, the smaller FMD response in DM2 is likely to be caused by impaired endothelial rather than smooth muscle cell function, as the NMD response was not impaired. Third, indices of hyperglycemia and hyperinsulinemia explained at most 2% of the association between DM2 and FMD. Taken together, our data support the hypothesis that impaired endothelial synthesis of NO may explain, at least partially, the increased cardiovascular disease risk in DM2, but does not support the existence of a similar mechanism in IGM.

Our investigation had important advantages over previous studies, which were relatively small and concerned selected populations. Additionally, to be able to adjust for potential confounders, we extensively characterized our population in terms of cardiovascular disease and risk factors.

The present and previous data suggest that impaired endothelial function in DM2 is a generalized phenomenon, which is neither restricted to the specific stimulus applied [11,14,23,27] nor to vascular territory [13,26,27], the type of vascular bed [9,16,27] or the type of endothelial dysfunction [42,43]. Surprisingly, the impaired FMD in DM2 could only be explained to a minor extent by indices of hyperglycemia or hyperinsulinemia. In contrast, some studies suggest that acute hyperglycemia and hyperinsulinemia may acutely impair FMD [44–46], although the data are not consistent [47] and may differ along the arterial tree [48]. Taken together, these [44–47] and the present data suggest that the effects of acute hyperglycemia and hyperinsulinemia may differ from those of more chronically elevated glucose and insulin levels. Indeed, there is evidence that endothelial cells can adapt to hyperglycemia [49,50]. Our results thus raise the possibility that other pathophysiological mechanisms are involved, such as chronic low-grade inflammation and increased oxidative and carbonyl stress [43,51]. Interestingly, Tan et al. [8] have recently shown that increased concentrations of advanced glycation end products were independently associated with impaired endothelium-dependent vasodilation.

Somewhat surprisingly, IGM was not associated with impaired FMD, although the confidence intervals in Table 3 do not entirely exclude impaired FMD in IGM. In addition, it is important to note that impaired brachial artery FMD denotes endothelial dysfunction with regard to a particular function (vasomotor regulation), a particular vascular bed (conduit artery), and a particular stimulus (shear stress). Normal FMD

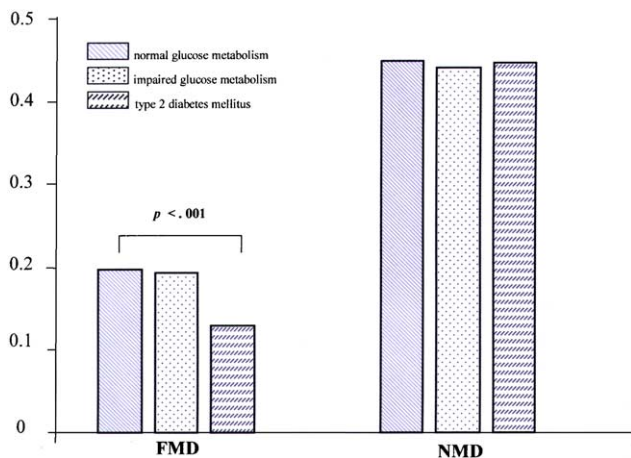


Fig. 1. Absolute change in diameter (mm) for flow-mediated dilation (FMD) and nitroglycerine-mediated dilation (NMD) according to glucose tolerance.

in IGM therefore does not imply that endothelial function in IGM is normal in general. In fact, there is considerable evidence that it is not [52,53]. Our findings in the present population are, however, in concordance with the observation that hyperglycemia and hyperinsulinemia were of limited value in explaining the association between FMD and DM2. These data also argue against the hypothesis that impaired FMD is an important mechanism linking IGM with increased cardiovascular disease risk. In contrast, we have recently shown that, like DM2, IGM is associated with increased arterial stiffness and arterial remodeling [35,54,55], suggesting that these processes may be important early determinants of cardiovascular disease risk in IGM, while impaired FMD may occur later.

Our study had several limitations. First, the method we employed to estimate FMD assumes that FMD is mostly or entirely NO-dependent, that exogenous administration of glyceryltrinitrate adequately mimics the effects of endogenous release of NO, and that there is no rightward shift of the glyceryltrinitrate dose–response relationship of vascular smooth muscle cells [56,57]. The validity of these assumptions remains to be established. Nevertheless, there is increasing evidence that impaired endothelium-dependent vasodilation, including impaired flow-mediated vasodilation, is associated with an adverse cardiovascular prognosis [58,59]. Secondly, we observed that ischemia-induced reactive hyperemia (i.e., the increase in flow and thus shear stress), expressed as percentage increase in peak systolic velocity, decreased with deteriorating glucose tolerance (Table 2). As age and hypertension were also negatively associated with the increase in peak systolic velocity (details not shown), and as age and hypertension are associated with microvascular rarefaction [17], the finding of decreased peak systolic velocity in IGM and diabetes may have been related to arteriolar and capillary rarefaction [17,27,60], which would decrease ischemia-induced microvascular dilatation and, consequently, the pressure drop over the brachial artery and the amount of reactive hyperemia. As a result, the increase in shear stress was slightly less in IGM and DM2 than in NGM. This issue, however, did not affect our results, as the differences were small and were adjusted for in the analyses. Thirdly, our findings were obtained in an elderly population characterized by the concurrence of several cardiovascular disease risk factors. Therefore, inferences to other populations (e.g., younger and/or with less cardiovascular disease risk factors) should be made with care. Finally, individuals with a high body mass index were less likely to participate, which may have resulted in an underestimation of the confounding role of body mass index. We consider this unlikely, however, as adjustment for body mass index had no effect whatsoever on the association between FMD and glucose tolerance (Table 3), despite the clear association between FMD and body mass index (Table 4).

In conclusion, we have shown that DM2 is associated with impaired FMD, whereas IGM is not. The mechanism behind

this association is unclear but does not appear to involve conventional cardiovascular risk factors, hyperglycemia or hyperinsulinemia. Impaired endothelial synthesis of NO may explain, at least partly, the increased cardiovascular disease risk seen in DM2.

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